Claim 53 is cancelled without prejudice since it was withdrawn from consideration as directed to non-elected subject matter. Applicants reserve all rights to prosecute the non-elected subject matter in a continuation or divisional application.

Claims 54-55 are cancelled without prejudice. Applicants reserve all rights to prosecute the subject matter of these claims in a continuation or divisional application.

New Claim 56 is added by amendment. As detailed below, new claim 56 is fully supported by the specification and claims as originally filed, in particular original Claim 37 and claim 6 upon which it depended. No new matter is added.

Upon entry of amendments herein Claims 37-39, 48-52 and 56 will be pending and under active consideration.

Objections

The drawings are objected to for informalities.

Submitted herewith, under separate transmittal, are formal figures which avoid the objection made. Hence, this objection must be withdrawn.

The specification is objected to for certain "informalities".

a) The Office Action asserts that the use of brackets [...] in the amendment to page 3 submitted on October 23, 2001 is confusing since "brackets [...] indicates deletion".

In reply, Attorney for Applicants respectfully submit that in Appendix A, *i.e.*, the "marked-up" version of the specification as amended on October 23, 2001, it was clearly indicated that "strike-out" indicated deletion and brackets did not. In an effort to advance prosecution, Attorney's for Applicants have again amended the text on page 3 to delete the brackets which were part of the specification as originally filed. In the "marked-

up" version of the text submitted herewith, it is noted that "strike-out", not brackets indicates deletion. The specification, as amended, no longer contains brackets.

b) The Office Action indicates that use of trademarks has been noted.

In reply, the text of the specification has been amended at pages 42, 46 and 47 to indicate the trademarks mentioned therein.

c) The Office Action asserts that at pages 41-42, the specification improperly attempts to incorporate a Genebank sequence which is alleged to be "critical or essential" to practice of the present invention.

Firstly, the statement on pages 41-42 "The *E. coli* DegP (Htra) amino acid sequence available from Gene Bank" even together with the statement at page 50 that "Various publications were cited herein, the disclosure of which are incorporated by reference in their entirety" does not constitute any attempt at incorporation by reference. Moreover, even if it did, the DegP sequence is not essential to practice the invention as currently claimed. Hence, this objection is moot and should be withdrawn.

Attention is directed to the language of Claim 37. As presently amended, Claim 37 recites that the isolated NGSP polypeptide of the invention "specifically binds an antibody that specifically binds a polypeptide encoded by the nucleotide sequence of SEQ ID NO. 3". The amino acid comprising an amino acid sequence of SEQ ID NO. 4 is a specific example of a polypeptide encoded by the nucleotide sequence of SEQ ID NO. 3. Recitation of any comparison to the sequence to DegP is no longer made in Claim 37 and is not necessary either to distinctly point out the invention or to distinguish over the prior art.

Attention is further directed to Exhibit 1, pages 1-4, attached hereto. Exhibit 1 presents the results of BLAST comparisons between the amino acid sequence of

present SEQ ID NO. 4 and the amino acids sequences of two polypeptides taught in the Gilbert reference (already of record in the file of this application).

More particularly, Exhibit 1, pages 1-4, summarizes and illustrates results of BLAST comparisons between the amino acid sequence of *Neisseria* polypeptides of U.S. Patent No. 6,096,529 to Gilbert (Gilbert) and specific examples of the presently polypeptide encoded by presently claimed SEQ ID NO. 3 (as recited in Claim 37).

Most specifically, Exhibit 1, pages 1 and 2, respectively, summarize and present results of a comparison between the amino acid sequence SEQ ID NO. 4 of Gilbert and amino acid sequence SEQ ID NO. 4, encoded by the present nucleotide sequence SEQ ID NO. 3. As shown, there was no significant similarity.

Exhibit 1, pages 3 and 4, respectively, summarize and present results of a comparison between the amino acid sequence SEQ ID NO. 2 of Gilbert and the amino acid sequence SEQ ID NO. 4 encoded by the present nucleotide sequence SEQ ID NO. 3. As shown, there was no significant similarity.

d.) The Office Action indicated that the specification at page 3 should be amended to identify the referenced co-pending application by application serial number rather than attorney docket number.

In response, page 3 is amended to recite the proper application serial number.

In light of the above and present amendments, it is submitted that all outstanding objections are avoided and should be removed.

Rejections Under Section 101 and Section 112, 1st paragraph

Claims 37-39, 48-52, 54 and 55 are rejected under Section 101 as allegedly not supported by a specific, substantial or well established utility. The Office Action reviews the teaching of the specification in several sections and asserts that the "asserted credible utility of the polypeptide encoded by the claimed nucleic acid or a fragment thereof is diagnostic, therapeutic and/or prophylactic. However the claimed nucleic acid... [is] not supported by a specific utility, because the asserted uses of the nucleic acid...are not specific to *Neisseria* in general, or to specific species of *Neisseria*."

Applicants emphatically disagree and respectfully submit that the present specification clearly presents at least one credible, specific utility for the presently claimed isolated nucleic acids, i.e., to encode an NGSP polypeptide which is useful to induce an immune response against infection by *Neisseria gonorrhoeae*. See the specification at page 1, lines 11-24; particularly at lines 19-21; page 4, lines 16-18 and line 35 through page 5, line 8, etc.

First, as made crystal clear by the Court of Appeals for the Federal Circuit, an application need only make one credible assertion of a specific utility to satisfy the requirement of Sections 101 and 112 with respect to utility. See, e.g., *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958 (Fed. Cir. 1983), *cert. denied.*, 469 U.S. 1984 ("When a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown".) Indeed, the court has explained that additional statements regarding utility, even if not credible, do <u>not</u> negative satisfaction of the requirements. See, e.g., *In re Gottlieb,* 328 F.2d 1016, 1019 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for other further purposes "indicated" in the specification"), *accord, In re Malachowski*, 530 F.2d. 1400 (CCPA 1976); *Hoffman v. Klaus,* 9 U.S.P.Q. 2d 1657 (Bd. Pat. App. & Int. 1988).

In the present situation, as explained above, the specification explicitly states that the claimed isolated nucleic acids are useful to encode an NGSP polypeptide which is useful to induce an immune response against infection by *N. gonorrhoeae.* Such assertion constitutes one credible specific utility and hence fully meets the Section 101 and 112 requirements for utility.

Second, attention is directed to the Declaration under 37 C.F.R. §1.132 of Dr. W. James Jackson (Jackson Declaration) with attached Exhibit A submitted herewith.

Dr. W. James Jackson is a co-inventor of this application. As stated in the Jackson Declaration, certain experiments were conducted, under his supervision and control, which clearly demonstrate that the isolated *Neisseria* polypeptide designated "NGSP" polypeptide taught in the application is useful to induce an immune response against infection by *Neisseria gonorrhea.* (Jackson Declaration, ¶¶2, 5). An art accept murine model of vaginal colonization, as described in Jerse, 1999, Infec. Immun. 67(11): 5699-5708, was used to evaluate the ability of the isolated NGSP polypeptide of the invention to induce an immune response. Id., ¶ 3, see Exhibit A.

Recombinantly expressed isolated NGSP polypeptide as taught in the application was used as immunogen; inactivated whole cell *N. gonorrhea* antigen was used as positive control and PBS was used as negative control. Id., ¶¶ 3a-3c; also Table 1. Animals were challenged with *N. gonorrhea* three to five days after the last administration of antigen or control. Id., ¶¶ 3d-3e. At 48hrs post challenge the level of *N. gonorrhea* vaginal colonization was assessed by swabbing the vaginal canal with pediatric nasopharengyl Dacron/Polyester swabs to collect infectious microorganisms. Swabs were removed, moistened by brief immersion into sterile PBS used to streak plate Thayer Martin chocolate agar plates containing antibiotics (vancomycin, colistin, nystatin, timethoprim).

A standard quantitative dilution streak plating method was used to enumerate colonies. Plates were incubated at 37°C under oxygen depleted or microaerophilic conditions for 24 to 72 hours prior to counting. Protective efficacy is expressed as percent of animals protected in a vaccination group. Id., ¶ 3f.

Results are presented in Table 2 of the Jackson Declaration. As explained by Dr. Jackson, fewer mice immunized with isolated recombinant NGSP polypeptide were found to be infected with *N. gonorrhea* after challenge compared to the unimmunized and unprotected negative controls. The level of protection conferred by NGSP polypeptide of the invention is equivalent to that obtained with the positive control, i.e., inactivated *N. gonorrhea* whole cell antigen. Id., ¶ 5.

As concluded by Dr. Jackson: "These results clearly demonstrate that isolated NGSP polypeptide of the present application can confer protection against vaginal infection by *N. gonorrhea*. These results demonstrate that the isolated NGSP polypeptide is useful to induce a protective immune response against *Neisseria gonorrhea* in a relevant animal model and thus is useful for a protective human vaccine." Id.

Based on the results presented in the Jackson Declaration and the remarks above, it is submitted that the rejections based on Sections 101 and 112, 1st paragraph should be withdrawn.

Section 112, 1st Paragraph Rejections

Claim 39 and Claims 50-52 dependent thereon are rejected as containing new matter in the recitation of "0.25mM NaCl". The Office Action indicates that the specification at page 25, line 7 supports the recitation "0.25M" NaCl not "0.25mM" NaCl.

Accordingly, Claim 39 has been amended to recite the proper concentration of NaCl, i.e., "25M NaCl" as taught in the specification. Hence, this rejection is avoided.

Claim 55 is rejected as not supported for the recitation "serine protease motiff".

While Applicants do not agree and in no way acquiesce with this rejection or the grounds in which it is based, merely to advance prosecution and obtain coverage for certain embodiments of the invention, Claim 55 is cancelled herein without prejudice. All rights to prosecute the subject matter of the claim in a continuation are reserved. Hence this rejection is moot and must be withdrawn.

In view of the above, it is submitted that all rejections based on Section 112, 1st paragraph are avoided.

Section 112, 2nd Paragraph Rejection

Claims 37-39, 48-52 and 54 are rejected under Section 112, 2nd paragraph.

a) Claim 37 is rejected as allegedly indefinite with respect to the recitation that the polypeptide has "about 36% sequence identity to DegP protein".

While Applicants do not agree and in no way acquiesce with this rejection or the grounds on which it is based, merely to advance prosecution, Claim 37 is amended to recited that the "polypeptide specifically binds to an antibody that specifically binds to a polypeptide encoded by the nucleotide sequence of SEQ ID NO.: 3". Support is found in the specification, e.g. at page 12, lines 8-22, at page 23, lines 20-32, etc., and original Claim 37, dependent upon original Claim 6.

b) Claims 38 and 39 are rejected as allegedly vague in the recitation of "the sequence of SEQ ID NO.: 3" without reciting that the sequence is a "nucleotide" sequence.

In order to avoid the rejection, these claims have been amended to recite specifically that the sequence is a "nucleotide sequence" as is obvious from SEQ ID NO. 3 in the Sequence Listing.

c) Claim 37 is rejected as allegedly vague in the recitation of "about 36%". Although Applicants do not agree with this rejection or the grounds on which it is based, and while preserving all rights to prosecute the subject matter is a continuation application, as indicated above, Claim 37 has been amended to avoid this recitation.

d) Claims 48, 49 and 54 are rejected as allegedly vague in the recitation of "encoded by SEQ ID NO.: 3" without specification that the sequence is a "nucleotide sequence".

With all due respect, Applicants submit that such recitation is not necessary. As clearly indicated in the Sequence Listing of the application, SEQ ID NO.: 3 is a "DNA sequence" made up of nucleotides. Thus, one of skill in the art reading Claims 48 and 49 in light of the rest of the application, including the Sequence Listing, would surely understand that SEQ ID NO.: 3 is a "nucleotide" sequence. Hence, there is no need to amend claims 48 and 49 which have not previously been amended. As indicated above Claim 54 has been cancelled without prejudice.

e) Claim 50 is alleged to have improper antecedent basis for the recitation "the isolated DNA" because the parent claims are indicated not to recite any "DNA".

Applicants have reviewed present Claim 50 and note that it reads as follows:

"50 (once amended) A pharmaceutical composition comprising the isolated nucleic acid of any one of Claims 37, 38, 39, 48 or 49".

Each of Claims 37, 38, 39, 48 and 49 recite "An isolated nucleic acid...". Hence, there is proper antecedent basis for the present language of Claim 50.

f) Claims 50-52 dependent on Claims 37 and 39 are rejected as indefinite due to alleged indefiniteness of Claim 37.

As detailed above, Claims 37 and 39 are amended to avoid any alleged indefiniteness. Hence, these claims avoid this rejection.

g) Claim 39 remains rejected for the reasons set forth in paragraph 18 of the Office Action mailed May 7, 2001, i.e., for the use of abbreviations. The Office Action suggests providing the full term for each abbreviation with the abbreviation in parenthesis at the first occurrence of each abbreviation.

In response, the abbreviated terms have been identified at first occurrence in Claim 39. Hence, this rejection is avoided.

In view of the above, it is submitted that all Section 112, 2nd paragraph rejections are overcome, avoided or in error and must be withdrawn.

Section 102 Rejection

Claim 55 is rejected under Section 102(b) as anticipated by Halter et al 1989, EMBO J 8:2737 or Pohlner et al., 1987, Nature 325:458.

While Applicants do not agree and in no way acquiesce with this rejection or the grounds in which it is based, merely to advance prosecution and obtain coverage for certain embodiments of the invention, Claim 55 is cancelled herein without prejudice. All rights to prosecute the subject matter of the claim in a continuation are reserved. Hence this rejection is moot and must be withdrawn.

Conclusion

For reasons indicated above, it is submitted that all outstanding objections and rejections are overcome or avoided.

Respectfully submitted,

Date December 20, 2002

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Appendix A

Marked-Up Version of the Specification
Application No: 09/388,090

[Double underlining indicates addition and strike-out (not square brackets) indicate deletion]

Page 3, line 9:

One object of this invention is to identify and provide a novel and highly conserved protein (referred to hereafter and in the claims as "NGSP") from *Neisseria spp.*, preferably *Neisseria gonorrhoeae*, *Neisseria ovis*, *Neisseria lacunata*, *Neisseria osloensis*, and *Neisseria bovis*. The protein of the present invention has a molecular weight of approximately 40-55 kD, and has limited similarity (~36% identity overall) to the DegP (HtrA) protein of *E. coli* ([% identity determined using BLASTP program (Altschul et al., 1990, J. Molec. Biol. 215:403-10; Altschul et al., 1997, Nuc. Acids Res. 25:3389-3402) with data entered using FASTA format; expect 10 filter default; description 100, alignment) and has not been previously identified in any *Neisseria spp.* The protein sequence which is another object of this invention has similarity to several DegP/HtrA-like serine proteases from two other bacteria and these sequence homologies have not been previously reported for any *Neisseria spp.*

On page 3, line 25

The present invention encompasses the NGSP polypeptide of *Neisseria gonorrhoeae* and other *Neisseria spp,* including but not limited to, *Neisseria ovis, Neisseria lacunata, Neisseria osloensis,* and *Neisseria bovis,* having a molecular weight, as determined from the deduced amino acid sequence, of 40 kD to about 55 kD, in isolated or recombinant form. A homologous protein, NMASP, from *Neisseria meningitidis,* is described and claimed in copending application of Applicants entitled "*Neisseria meningitidis* Polypeptide, Gene Sequence And Uses Thereof" ~~[Attorney Docket No. 7969-083]~~ (Application No.: 09/388,089) filed on even date herewith, which is hereby incorporated by reference in its entirety. The present invention encompasses a purified NGSP polypeptide, polypeptides including fragments, derived therefrom (NGSP-derived polypeptides), and methods for

making said polypeptide and derived polypeptides. The invention also encompasses antisera and antibodies, including cytoxic or bacterial bactericidal antibodies, which bind to and are specific for the NGSP polypeptide, NGSP-derived polypeptides and/or fragments thereof.

At page 41, line 30

The *E. coli* DegP (HtrA) amino acid sequence available from GeneBank was employed as a BLAST (TBLASTN) subject query to search the genomic sequence databases for *N. gonorrhoeae* (Univ. Oklahoma, USA) strain 1090 to identify linear amino acid sequences that might share some similarity to the DegP protein. No predicted amino acid sequences from this *Neisseria* database showed more than ~30-35% similarity to the *E. coli* DegP protein sequence. Candidate *N. gonorrhoeae* NGSP amino acid sequences were localized within specific genomic DNA sequence "contigs", and putative open reading frames encoding these NGSP sequences were derived. Putative ORFs capable of encoding proteins of ~40-55 kD, the average size of most DegP-like serine proteases, were then selected and further analyzed for the presence and appropriate relative spacing of semi-conserved catalytic residues (H, D, S) thought to be required for serine protease activity. A single putative open reading frame from the *N. gonorrhoeae* database was identified which met these criteria.

At page 42, line 9

N. gonorrhoeae strain GC340 was obtained from the Centers for Disease Control and Prevention (CDC). GC340 was streaked on gonococcal agar base (GC agar™, Difco) containing 1.0% IsoVitale™ X (BBL) and grown at 35-37°C in 5% CO_2 for ~24-28 hours. To prepare confluent "lawns" of cells for DNA isolation, three or four single colonies were picked from the "overnight" seed plate and used to inoculate fresh GC plates which were again grown overnight at 35-37°C in 5% CO_2. Cells were collected from the surface of the agar plates by gentle rinsing using trypticase soy broth (TSB) containing 10% glycerol and then stored at -20°C. When needed, cells were thawed at room temperature and bacteria collected by centrifugation in a Sorval SS34 rotor at ~2000 Xg for 15 minutes at room

temperature. The supernatant was removed and the cell pellet suspended in ~5.0ml of sterile water. An equal volume of lysis buffer (200mM NaCl, 20mM EDTA, 40mM Tris-HCl pH8.0, 0.5% (w/v) SDS, 0.5% (v/v) 2-mercaptoethanol, and 250ug/ml of proteinase K) was added and the cells suspended by gentle agitation and trituration. The cell suspension was then incubated ~12hours at 50°C to lyse the bacteria and liberate chromosomal DNA. Proteinaceous material was precipitated by the addition of 5.0ml of saturated NaCl (~6.0M, in sterile water) and centrifugation at ~5,500 X g in a Sorval SS34 rotor at room temperature. Chromosomal DNA was precipitated from the cleared supernatant by the addition of two volumes of 100% ethanol. Aggregated DNA was collected and washed using gentle agitation in a small volume of a 70% ethanol solution. Purified chromosomal DNA was suspended in sterile water and allowed to dissolve/disburse overnight at 4°C by gentle rocking. The concentration of dissolved DNA was determined spectrophotometrically at 260nm using an extinction coefficient of 1.0 O.D. unit ~50ug/ml.

At page 46, line 13

A general process for the purification of NGSP protein as a soluble protein is given below. Insoluble material is removed after French press disruption by high speed centrifugation (~10,000Xg, 4°C, 30min). The soluble fraction containing NGSP is suspended in ~20ml of ice cold 50mM Tris-HCl buffer (pH8.0) and loaded onto a DEAE-SEPHACEL™ (Diethylaminoethyl cellulose) (Pharmacia) ionic exchange column (~5cm X 60cm). To minimize autoproteolysis of the NGSP protein, chromatography is conducted at 4°C. Unbound material is washed from the column using loading buffer (50mM Tris-Hcl, pH8.0) prior to elution of bound NGSP protein. Elution of NGSP from the SEPHACEL™ (cellulose) matrix is achieved using a NaCl gradient (0.05 - 0.5M NaCl, in 50mM Tris-Hcl, pH8.0). Fractions released by the salt gradient are collected and examined by standard SDS-gel electrophoresis methodologies for the presence of a ~40-55 kd protein. Fractions are also assayed for protease activity using a standard azocasein colorimetric assay. Fractions

containing NGSP are pooled and extensively dialyzed against 10mM sodium phosphate buffer (SPB, pH8.0) at 4°C.

At page 47, line 5

The sequence information shown above is used to design a pair of nondegenerate convergent (i.e., one forward and one reverse primer) oligonucleotide primers. PCR amplification of DNA fragments is performed under the same conditions as described above with the exception that the annealing temperature is raised to 50°C. The DNA fragment is isolated from an agarose gel as before and readiolabelled using (32P)-gamma-ATP and T4 polynucleotide kinase according to standard methods. Unincorporated radiolabel is separated from the probe on a G25 ~~Sepharose~~ SEPHAROSE™ (Agarose) spin column. Before use, the probe is denatured for 2 min. at 95°C and subsequently chilled on ice (4°C).

Appendix C

Marked Up Version of the Claims
Application No: 09/388,090
Docket No.: 7969-082-999

[Addition indicated by underlining deletion indicated by brackets]

37. (Four Times Amended) An isolated nucleic acid comprising a nucleotide sequence encoding an isolated non-cytosolic polypeptide of a *Neisseria* spp. (NGSP) polypeptide, which is a polypeptide of a *Neisseria* species with the proviso that said *Neisseria* species is not *N. meningitidis*, which polypeptide has a molecular weight of about 40 kD to about 55 kD as determined in SDS polyacrylamide gel electrophoresis using glutamic dehydrogenase, carbonic anhydrase and myoglobin-blue as molecular weight markers, and which polypeptide [has about 36% sequence identity to Deq P protein of *E.coli* when % sequence is determined using a BLASTP program using FAST format, expect 10 filter default, description 100] specifically binds an antibody that specifically binds to a polypeptide encoded by the nucleotide sequence of SEQ ID NO. 3.

38. (Four Times Amended) An isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO. 3.

39. (Thrice Amended) An isolated nucleic acid encoding a NGSP *Neisseria sp.* polypeptide which comprises a nucleotide sequence that hybridizes at 68°C in 0.5M $NaHPO_4$ (pH 7.2) 1 mM ethylendediaminetetra acetic acid (EDTA)/7% SDS or at 65°C in 6X sodium chloride/sodium citrate (SSC), 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% polyvinyl pyrol PVP, 0.02% Ficoll, 0.02% BSA or in 50% formamide/0.25 M $NaHPO_4$ (pH 7.2)/0.25 [m]M NaCl/1 mM EDTA/7% SDS to the sequence of nucleotide SEQ ID NO. 3 or

the complement thereof, wherein said complement is complementary to at least 25 contiguous nucleotides of SEQ ID NO. 3.